REMARKS

Applicants' representative would like to thank the Examiner for his time and consideration in conducting an Interview on June 16, 2010, during which amendments to the claims regarding a linker that couples the therapeutic protein with the transport aid in a pH dependent manner was discussed. It is noted that the Athappilly *et al.* reference, which is limited to the purification of compounds conjugated to streptavidin or iminobiotin under mild conditions by affinity chromatography, was submitted in an Information Disclosure Statement of July 28, 2004.

Claims 1-7, 9-10, 12, 14, 16-21, 23-26, 28-34, 44-49, 51-52, 54-60, 62-63, 65-66, 68-75 and 129-134 are presented for examination.

Claims 8, 11, 13, 15, 22, 27, 35-43, 50, 53, 61, 64, 67 and 76-128 are canceled without disclaimer or prejudice. New Claims 129-134 are added.

Claims 1, 28 and 54 are currently amended to recite that the streptavidin-biotin complex "links the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH." The amendments are supported by paragraph [0075] of the specification, which teaches that the linker serves to bind the protein and transport aid in the neutral pH environment of the cerebral spinal fluid (CSF) but disassociates once taken up by the cells, whereby the protein is released and delivered to the target site. New Claims 129-134 recite additional limitations to the streptavidin-biotin complex of Claim 1, which are supported at least by paragraphs [0075] and [0087] of the specification. No new mater has been added, and entry is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Office Action rejected Claims 1-6, 9-10, 12, 14, 18-21, 23-26, 28-33, 45-49, 51-52, 54-59, 62-63, 65-66, and 69-75 as being unpatentable over U.S. 5,814,014 (Elsberry *et al.*) in view of U.S. 5,433,946 (Allen *et al.*) and of U.S. 2003/0129186 (Beliveau *et al.*). However, the *prima facie* case of obviousness has not been established over the pending claims because (1) Elsberry *et al.* fails to teach the limitation of a genetic sequence of the patient's gene encoding for the protein to be delivered as one of the factors for the programmable delivery route, and (2) the references fail to teach or suggest a streptavidin-biotin complex linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

In particular, Beliveau *et al.* teaches that a streptavidin-biotin complex can be used as a label, which can be optionally attached to a component for radio-labeling. However, it does not teach that the streptavidin-biotin complex can be used for any purpose other than for marking or labeling or that the streptavidin-biotin complex itself can be used to link a therapeutic protein and a transport aid together. In fact, Beliveau *et al.* expressly teaches at paragraph [0187] that the linker is not a critical aspect of the invention.

In contrast, the presently pending claims recite that the linker can be a streptavidin-biotin complex and that it may be used to link the therapeutic protein with the transport aid in a pH-dependent manner such that the therapeutic protein and transport aid remain operably linked at the neutral pH environment of the CSF but can become dissociated once taken up by cells into lysosomal compartments or other acidic intracellular organelles. This pH-dependent aspect of

the claimed linker complex demonstrates the unexpected effect of the claimed invention, whereas Beliveau *et al.* teaches away from the present invention by indicating that the inclusion of the streptavidin-biotin linker is not critical.

The Office Action also rejected Claims 7, 16-17, 34, 44, 60 and 68 as being unpatentable over Elsberry *et al.* in view of Allen *et al.* and Beliveau *et al.*, and further in view of U.S. 6,015,572 (Lin *et al.*). Regarding Claims 7, 34 and 60, the Office Action alleged that Lin *et al.* teaches GDNF, FMRP and combinations thereof. However, insofar as the independent base claims are patentable over the other references, as set forth above, these dependent claims are also nonobvious.

Regarding Claims 16-17, 44 and 68, the Office Action alleged that Lin *et al.* teaches that the therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation and that the integrity and activity of the protein formulation is achieved by adding at least one species operable for maintaining a desired pH to the therapeutic protein formulation. However, the species taught by Lin *et al.* for maintaining pH is distinct from the streptavidin-biotin linker of the presently pending claims because the species of Lin *et al.* maintain the pH of the therapeutic protein formulation, whereas the linker of the claimed invention is pH-dependent such that the entire claimed complex of the therapeutic protein and transport aid remain operably linked at the neutral pH environment of the CSF but can become dissociated once taken up by cells into lysosomal compartments or other acidic intracellular organelles. Therefore, Lin *et al.*, like Beliveau *et al.*, Allen *et al.* and Elsberry *et al.*, does not teach or suggest the claimed linker complex.

Double Patenting

The Office Action rejected Claims 1-2, 4, 28-29, 31, 54, 55 and 57 on the grounds of non-statutory obviousness-type double patenting over Claim 1 of Elsberry *et al.* Further, these claims and Claim 74 were rejected based on Claims 1, 3, and 11 of U.S. 6,056,725 (Elsberry *et al.* '725). The Office Action stated that the lack of a streptavidin-biotin complex as a linker in the cited patent is not persuasive for overcoming the double patent rejection, because substituting the drug for protein, whether modified with a streptavidin-biotin complex or not, would be obvious to one skilled in the art. However, the patented claims are demonstrably different from those pending in the present application. In particular, Claim 1 of Elsberry *et al.*, recites a system comprising (1) an implantable pump and a drug capable of altering the level of excitation of neurons in the brain related to degenerating neurons and (2) a sensor for generating a signal related to an attribute of said nervous system which indicates the hyperexcitation of said degenerating neurons or of neurons related to said degenerating neurons. Aside from a superficial similarity of an implantable pump, presently pending Claim 1 is patentably distinct from Claim 1 of Elsberry *et al.* due to the recitation of therapeutic proteins modified by conjugation to a transport aid that facilitates cellular uptake wherein a linker between the therapeutic protein and transport aid is a streptavidin-biotin complex. Nothing in Elsberry *et al.* '725 would motivate one of ordinary skill to make the presently claimed invention.

Similarly, Claims 1, 3 and 11 of Elsberry *et al.*, '725 relate to a distinct invention: Claim 1 recites a catheter system for delivering indomethacin to a selected site within a hippocampus or lateral ventricle, comprising a pump, a source of indomethacin in fluid communication with the pump, and a catheter; Claim 3 recites subcutaneous placement; and Claim 11 recites a catheter

system for delivering a nonsteroidal anti-inflammatory agent comprising a pump, a source of nonsteroidal anti-inflammatory agent, and a catheter. There is no teaching or suggestion that substituting the drug for the therapeutic protein formulation of the present invention would be desirable.

Finally, by the Office Action's own admission, the presently pending claims are neither anticipated by nor obvious over either Elsberry patent alone, and, hence, the present invention cannot be patentably indistinct from those patents.

Conclusion

In light of the foregoing, it is submitted that the application is now in condition for allowance. It is therefore respectfully requested that the rejections be withdrawn and the application passed to issue.

Respectfully submitted,
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